REMARKS

Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-124 are currently active.

The Examiner has rejected Claim 1 under 35 U.S.C. 112 as being indefinite. Claim 1 has been amended to obviate this rejection.

The Examiner has rejected Claims 1, 51, 57, 70, 74, 75 and 80 under 35 U.S.C. 112 as being indefinite. These claims have been amended as the Examiner has suggested.

The Examiner has rejected Claims 48 and 49 as being indefinite. The Examiner questions how the limitation of "compares images to each other serially" further limits the apparatus, structurally. This is well known standard patent law in regard to apparatus claims and that the structure specifically is physically required to compare images to each other serially. This is clear and definite to one skilled in the art. The limitation further limits how the structure operates. This is fundamental to any computer or software patent, let alone in regard to any element that is further limited in the way it is required to operate. Accordingly, Claims 40 and 49 are definite. Claim 96 has been amended to obviate the rejection against it.

Claims 49, 50, 94, 96 and 103 are now dependent on Claim 124, which obviates the rejections under 35 U.S.C. 112 against these claims.

Claims 51 and 99 have been amended to obviate the rejection under 35 U.S.C. 112 against them. Antecedent support for the change to Claim 99 is found on page 32, lines 3-6.

The Examiner has rejected Claims 1, 47, 48, 51-64, 70, 74-79, 94, 96, 103, 104 and 124. Applicants respectfully traverse this rejection. In order for claims to be anticipated, every element in every limitation of the claim must be found in the document itself that is cited as a basis anticipation. It is respectfully submitted that Findley does not meet this requirement.

Specifically, Claim 1 has the limitation of a mechanism for automatically determining the state of said individual cell of the plurality of cells over time. Findley does not teach or suggest this limitation whatsoever. The Examiner has recognized this fact and has tried to overcome this significant material defect that the term "automatically" has not been interpreted to be limited to a system that is automated. The specification has not defined this term to be limited to such. It is specially submitted by the applicants, that the common definition of the term automatically when used in conjunction with a mechanism for

automatically determining, specifically requires that the mechanism automatically determines the state of said individual cell of the plurality of cells in real time overtime. It is again standard patent law that unless the specification indicates otherwise, a standard definition of the term will be applied, and such definition here can only be interpreted one way. This way is that the system as automated. This is how the applicants have chosen to write this claim and have so defined the claimed invention for the above-identified patent application. It is respectfully submitted that the examiner is completely ignoring standard patent law claim interpretation language to essentially ignore this critical term in applicants' claim.

Referring to Findley, there is disclosed an environmentally controlled in vitro incubator. Findley teaches the incubator 11 includes a chamber 13 which is enclosed by a transparent enclosure 15. Findley teaches that access by the user to the interior of the chamber 13 is provided by the hand openings 17 in the front face of the enclosure 15. Plastic cuffs 21 largely seal the hand opening 17 when not in use and seal the annulus between the users wrist or forearm and the edge of the openings during use to prevent contamination of the atmosphere within the chamber 13 by air. See column 4, lines 1-6.

A microscope 23 is mounted on microscope stage 25 and extends through an aperture 27 in the top of the closure 15 for permitting the user to examine biological materials being maintained within the chamber 13. See column 4, lines 9-15. There is provided an

airlock 57 for allowing the easy transfer of biological materials in culture dishes and other equipment between the chamber 13 and the ambient. See column 6, lines 38-42. A tray 63 is a slightly mounted on the tracks 64 within the airlock 57.

To further differentiate and emphasize this fact, applicants have introduced the limitation of a computer into the claims.

There is nothing taught or suggested whatsoever about a mechanism for automatically determining the state of the cell. Accordingly, Findley does not anticipate Claim 1, or any other claims of applicants.

The Examiner has rejected Claims 49, 51 and 114-123 as being unpatentable over Findley in view of Weinreb. Applicants respectfully traverse this rejection. As explained above, Findley does not teach or suggest what the examiner says it does. Weinreb does not add anything to the teachings of Findley.

Referring to Weinreb, there is disclosed an apertured cell carrier. Weinreb teaches a perforated cell carrier 1 that includes a base 3 in which are formed apertures or holes 2. The holes are arranged in rows and columns and have a larger opening at the tops than at the bottoms. The side walls of the apertures may converge continuously or in steps towards

the opening at the bottom side of the cell carrier. See column 7, lines 46-55. Weinreb teaches the shape of the apertures 2 enables the cells to be effectively held to the carrier by applying means, such as a pressure difference between the upper and the bottom side of the carrier, or electromagnetic forces. To first separate a particular group of cells from cells of other groups, since the cells in each group are of known size or sizes, which typically differ from those in other groups, the carrier 1 is chosen to have holes of sizes so that when the matter containing the various cell groups is placed on the carrier 1, effectively most if not all of the holes are occupied by cells of the group of interest, one cell per hole. See column 7, line 63-column 8, lines 6.

Weinreb teaches to load cells into the carrier. The carrier 1 is held in place above orifice 150 and plate 152 by means of collar 154 of solution basin 156. The collar presses the carrier against the portion of plate 152 which surrounds orifice 150 and creates a seal between that portion and the carrier. This seal prevents substantial numbers of cells from passing around the edges of the carrier, rather then being captured in the apertures. Orifice 150 is connected by outflow tube 160 to pump 162. The pump serves to produce a pressure differential across carrier 1 which pulls the cells into the apertures in the carrier. A basin 156 is configured so as to allow microscope objective 158 to be brought close enough to carrier 1 so that the apertures and the carrier can be brought into focus. Solutions are provided to basin 156 by one or more inflow tubes 164 which can be connected to syringe needles 166. The

inflow tubes are used to introduce various bathing and reagent solutions to basin 156. The inflow tubes are also used to wash excess cells off the top surface of carrier 1. Fluid is removed from base in 156 by means of drain tube 170. See column 12, lines 30-64. If an electromagnetic field is desired to be used instead of a pressure difference to drive the cells into the carrier apertures and retain the cells in the apertures, the field is oriented perpendicular to the top surface of the carrier and the cells are charged accordingly. See column 15, lines 14-30. As is evident from the above description, Weinreb is interested in, and focused on separating groups of cells by filling the apertures with the desired cells of a chosen side. There is no teaching or suggestion anywhere by Weinreb of any type of a dynamically controlled environment system as found in the claimed invention. As is also evident, there is no teaching or suggestion of any automated process for determining the state of said individual cell of a plurality of cells over time, as is found in the claimed invention of applicants.

Accordingly, Claims 49, 51, 114-123 are patentable over Findley in view of Weinreb.

The Examiner has rejected claims 80, 81, 86-93, 95, 97, 99 and 100 as being unpatentable over Findley in view of Weinreb and Early. Applicants respectfully traverse this rejection.

Early is presented by the examiner simply for teaching a robotic arm. Early does not add anything in relevant part to the teachings of Findley and Weinreb to arrive at applicants' claimed invention. Accordingly, these claims are patentable over the applied art of record.

The Examiner has rejected Claims 114-123 as being anticipated by Maruhashi. Applicants respectfully traverse this rejection. The claims have a limitation where an individual cell of the plurality of cells can be examined over time. Maruhashi does not teach or suggest this limitation. The Examiner in the "Response to Arguments" section states that the device of Maruhashi does not teach that all cells are analyzed, but that the device of Maruhashi could be used for such. This is not patent law. Patent law requires that the references teaches or suggests to do so, and Maruhashi has no capability of tracking each cell over time. Maruhashi has no ability to analyze each cell over time. From each picture to the next, Maruhashi cannot link the cell, nor does Maruhashi need or want to.

Referring to Maruhashi, there is disclosed a method and apparatus for investigating and controlling an object. Maruhashi teaches there is a relationship between shapes of cells and the activities of cells. See column 5, lines 58-69. By identifying the different shapes and counting the number of respective shapes in the sample, the ratio of secreting cells can be extrapolated and obtained for an entire population. See column 6, lines

18-20. Based upon the recognition of the shape of the cell being indicative of the activities of the cell, Maruhashi teaches a image recognition control system. The system is comprised of a tank 10 which contains liquid containing living bodies in suspension. Maruhashi teaches that a part of the liquid is withdrawn from the tank 10 and passed to an image pick-up device 20. An image of the part of the liquid is taken. Whatever cells are in the part are in the image but there is no control over which cells are in the part of the liquid. For any cell to actually be in the part is by chance and is arbitrary. This is because Maruhashi is concerned with large numbers of cells and what happens generally to all the cells, not "each" cell, or even any one cell "over time". It isn't possible for Maruhashi to monitor even one cell over time since the cells become lost in the liquid with the other cells. There is no teaching to mark or identify even one cell in Maruhashi to be able to monitor its state over time. The image pick-up device optically magnifies the image and stores it electrically as an image from a television camera. See column 8, lines 35-46. Maruhashi teaches that there is a transparent container 21 formed of glass or plastic in which the subject liquid is fed for observation from the liquid tank 10 to the container. See column 81, lines 58-62.

In another embodiment, Maruhashi teaches that a driving signal issues from a timer 33 causing liquid containing cells in suspension to be sampled and fed to the image pick-up device 20. See column 9, lines 14-18. In yet another embodiment, Maruhashi teaches a culture liquid sampled from a cell culturing tank is fed to image pick-up devices 26 and 27.

The image pick-up device generates picture emerges for observing cells. See column 10, lines 20-25. In another embodiment, Maruhashi teaches that the culture liquid is sampled from the cell culturing tank 10 and fed to an image pick-up device 20 where pictures of the cells are taken. See column 11, lines 4-9. In another embodiment, Maruhashi teaches a timer 33 generates driving signals which drive a pump of an image pick-up device 20. A culture liquid is sampled from a cell culture tank 10 and fed to an image pick-up device 20 where pictures are taken of the cells. See column 11, lines 26-33. In still another embodiment, Maruhashi teaches that the culture of liquid is sampled from the cell culture tank 470 and fed to an image pick-up device 420 where images of the culture of liquid are taken. See column 15, lines 27-33. In another embodiment, Maruhashi teaches a timer generates drive signals which drives the pump of the image pick-device 420. The culture liquid is sampled from the cell culture tank 470 and fed to the image pick-up device 420 where pictures are taken of the images. See column 15, lines 53-60. In yet another embodiment, Maruhashi teaches a pump 507 is operated to separate broth from the culture vessel 506 via the cell separator 505 and the duct 504, and separated broth is then passed to a collecting tank 508. An image pick up device 509 monitors the cells, where the image pick up device 509 operates in like manner corresponding to that described above for the earlier embodiments. See column 16, lines 32-39.

There is no teaching or suggestion of examining any single cell over time or the ability to examine any cell over time and know the cell had been previously imaged.

Maruhashi teaches in lines 18-53 of column 16 only that the broth and batches of cells are in the culture vessel and many cells at once are imaged. However, there is no teaching about identifying an individual cell, or how one cell could be examined over time in the midst of all the others cells in the same culture vessel to determine any single cell's state over time.

The goal of the apparatus taught by Maruhashi, as described in column 8, is to increase concentration of active living bodies to be useful in production systems for activated sludge and sewage treatment. In column 11, the apparatus is described to measure density of cells in liquid. In column 16, the final paragraph, it is described as being applicable to the flame in a furnace! All this also evidences that Maruhashi is only interested and only capable of macroscopic attributes formed from smaller units, but is not interested in the smaller units themselves over time.

While Maruhashi is composed of different separate components, they are connected together and could be considered one system. However, in regard to the claims, as amended, with the limitation of monitoring the cell over time, all the teachings of Maruhashi which require a part of the liquid to be moved evidence the fact that no cell can be monitored over time. This is because the cells are all intermingled with each other as they are transferred to the image device and then back to the tank. Additionally, the fact that parts of the liquid are transported with many cells but not individual cells or one cell at a time also evidences that

Maruhashi cannot monitor an individual cell over time to identify its state. In fact, the need to transfer parts of the liquid with many cells so an image of many cells can be taken at one time to obtain a representative sampling of the state of all the cells in the tank actually teaches away from monitoring a single cell over time. This is because monitoring a single cell over time would require many individual cells to be monitored to yield the same result, which Maruhashi has no capability to perform.

Applicants' Claim 114, as amended, has the limitation of a "an image recognition system for analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers, the image recognition system utilizing image recognition software". Maruhashi only teaches to view groups of cells at a time by an image-pick up device. Claims 114-123 are patentable for similar reasons over Maruhashi.

The Examiner has rejected Claims 114-123 as being unpatentable over Matsuzaki. Applicants respectfully traverse this rejection. The claims have the limitation where the state of an individual cell of the plurality of cells can be analyzed over time. Matsuzaki does not teach or suggest this limitation. Matsuzaki has no ability to analyze each cell over time. From each picture to the next, Matsuzaki cannot link the cell, nor does Matsuzaki need or want to.

Referring to Matsuzaki, there is disclosed an apparatus and method of culturing and diagnosis of animal cells using image processing. Matsuzaki teaches that the size of cells indicates whether they are living cells, dead cells and division potential-possessing cells. See column 4, lines 37-52. Matsuzaki teaches an apparatus comprises a culturing vessel 1, a culture medium observing portion 2, means 3 of introducing a culture medium to the observing portion 2, a measuring device 4 to measure sizes of cells in the observing portion 2, an analyzer 8 to determine a proportion of division potential-possessing cells or a portion of living cells on the basis of a cell size distribution, and means 6 to return a culture medium in the observing portion 2 to a culture medium in the culturing vessel. Figure 3 shows that the observing portion 2 is separate and apart from the culture vessel 1. Matsuzaki teaches the culture medium in the culturing vessel is partially fed to the observing portion 2, and cells in the partially fed culture medium in the observing portion 2 are measured by the measuring device 4 for a cell size distribution. When the measurement is finished, the culture medium in the observing portion 2 is returned to the culturing vessel 1. See column 5, lines 23-47.

Matsuzaki teaches the culture medium is intermittently fed from the culturing vessel 1, to the measuring portion 2. The culture medium can also be measured while it is fed continuously to the measuring portion 2. See column 5, lines 52-56.

Matsuzaki teaches the observing portion cell 2 has a cell structure which is formed by using a spacer 11, a film which is placed between 2 glass sheets 12 and 13. The cell is provided with an inflow tube 14 of a cell culture medium and an outflow tube 15 thereof. See figure 14 and column 10, lines 45-55. The culture medium is introduced into the cell by the inflow tube 14 from a circulation pipe connected to the culture vessel, and the stage and an observing device are manipulated to observe sizes of animal cells. See column 10, lines 63-67. The culture medium containing the measured cells is returned to the culturing vessel through the outflow tube 15. See column 11, lines 5-8. There is no teaching or suggestion in Matsuzaki how to separate a cell from the other cells it is with, either physically or with markers, to be able to determine the state of the cell over time.

From all the teachings of Matsuzaki, it is clear that the culture medium with the cells is fed to an observing portion 2. There is no teaching or suggestion of a "mechanism for incubating the plurality of cells . . . in which each individual cell of the plurality of cells can be examined over time . . . ; and a mechanism for automatically tracking and identifying said individual cell from the plurality of cells over time . . . ", as found in Claim 57 and for the reasons more fully elaborated upon above in regard to Maruhashi feeding cells to an imaging device. Accordingly, Claims 114-123 are not anticipated by Matsuzaki and are patentable over Matsuzaki.

Claim 47 has the limitation that the imaging mechanism includes a mechanism for phase contrast imaging to identify the state of each cell. The applied art of record does not teach or suggest this limitation.

Claim 48 has the limitation that the phase contrast imaging compares images to each other serially to identify the state of the cells. The applied art of record does not teach or suggest this limitation.

Claim 49 has the limitation that the imaging mechanism acquires two successive fluorescent images of each cell and compares them to each other serially to identify the state of each cell. The applied art of record does not teach or suggest this limitation.

Claim 50 has the limitation that the imaging mechanism includes antibody type labels with different colors of dyes for use to detect the presence of cell surface markers. The applied art of record does not teach or suggest this limitation.

Claim 52 has the limitation that the determining mechanism includes a mechanism for determining a biological event in the cell. The applied art of record does not teach or suggest this limitation.

Claim 53 has the limitation that the determining mechanism includes a mechanism for determining when a cell has doubled. The applied art of record does not teach or suggest this limitation.

Claim 54 has the limitation that the determining mechanism includes a mechanism for determining what state a cell is in with respect to doubling. The applied art of record does not teach or suggest this limitation.

Claim 55 has the limitation that the determining mechanism includes a mechanism for determining the stage of the cell based on a metabolic process the cell is experiencing. The applied art of record does not teach or suggest this limitation.

Claim 56 has the limitation that the determining mechanism identifies the production or the duration of proteins, simple or complex sugars, individual amino acids, individual ions, or individual molecules with respect to both physical presence and biological activity of the cell. The applied art of record does not teach or suggest this limitation.

Claim 58 has the limitation that the incubating mechanism includes a first well in which a first cell is disposed and a second well in which a second cell is disposed, and including a mechanism for controlling the division and the differentiation of the first cell and

the second cell while the cells are in the incubating mechanism. The applied art of record does not teach or suggest this limitation.

Claim 59 has the limitation that the controlling mechanism controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell while the cells are in the incubating mechanism. The applied art of record does not teach or suggest this limitation.

Claim 61 has the limitation that the controlling mechanism includes a mechanism for limiting differentiation of the daughter cells of the first cell. The applied art of record does not teach or suggest this limitation.

Claim 62 has the limitation that the identifying mechanism includes a mechanism for assessing synergistic or antagonistic effects of different combinations of factors on the cells.

Claim 63 has the limitation that the identifying mechanism includes a mechanism for identifying kinetic data for rates of cell division and differentiation. The applied art of record does not teach or suggest this limitation.

Claim 64 has the limitation that the controlling mechanism controls the cell with transcriptional regulators and regulators associated with adherence in cell differences based on time. The applied art of record does not teach or suggest this limitation.

Claim 77 has the limitation that the incubating mechanism includes m wells, where m is greater than or equal to 2, and the cell is disposed in a first of the m wells, and the exchanging mechanism exchanges n media in the first cell. The applied art of record does not teach or suggest this limitation.

Claim 79 has the limitation that there is a mechanism for automatically testing for predetermined biological variables and engineered genes with respect to each cell. The applied art of record does not teach or suggest this limitation.

Claim 81 has the limitation that there is a supply of antigen and a supply of fluorochrome connected to the robotic mechanism so antigen or fluorochrome can be dispensed to the cells in the incubating mechanism. The applied art of record does not teach or suggest this limitation.

Claim 86 has the limitation that the incubating mechanism has wells which hold corresponding cells and wherein the robotic mechanism includes a pipette which transfers

media from individual cells to the determining mechanism at predetermined intervals. The applied art of record does not teach or suggest this limitation.

Claim 87 has the limitation that the robotic mechanism dispenses 1 to 95 microliters of media. The applied art of record does not teach or suggest this limitation.

Claim 88 has the limitation that there is a liquid handling system connected to the robotic mechanism and a mechanism for cleaning of a liquid handling system with wash cycles. The applied art of record does not teach or suggest this limitation.

Claim 89 has limitation that there are P additional pipettes in communication with the wells, each pipette can either aspirate or dispense liquid to the wells, where P is an integer greater than or equal to 2. The applied art of record does not teach or suggest this limitation.

Claim 92 has the limitation that the robotic mechanism includes a probe which, when placed in the well, identifies how much fluid is in the well. The applied art of record does not teach or suggest this limitation.

Claim 94 has the limitation that the imaging mechanism counts the number of cells in each well. The applied art of record does not teach or suggest this limitation.

Claim 95 has the limitation that the determining mechanism analyzes tissue culture media in a well with either biochemical, immuno chemical, biological or chemical assays. The applied art of record does not teach or suggest this limitation.

Claim 96 has the limitation that the imaging mechanism uses pattern recognition to correlate the state of the cell with a more particular metabolic process of the cell. The applied art of record does not teach or suggest this limitation.

Claim 103 has the limitation that the imaging mechanism recognizes when a cell doubles in the incubating mechanism by pattern recognition. The applied art of record does not teach or suggest this limitation.

Claim 104 has the limitation that the determining mechanism includes a plurality of dyes, each dye associated with a different cell surface marker, to identify cell surface markers on a cell. The applied art of record does not teach or suggest this limitation.

Claim 117 has the limitation that upon the termination of particular cellular characteristics of the cells, the system controller is prompted to actuate the liquid handling system to provide exchange of media to the cells. The applied art of record does not teach or suggest this limitation.

Claim 118 has the limitation that the liquid handling system aspirates, irrigates and dispenses the media to the cells. The applied art of record does not teach or suggest this limitation.

Claim 119 has the limitation that the liquid handling system further includes a plurality of pipettes for providing the exchange of media to the cells, the plurality of pipettes removable along x, y and z dimensions with respect to the plurality of cells housing containers. The applied art of record does not teach or suggest this limitation.

Claim 120 has the limitation that the stage displaces at least one of the plurality of cell housing containers with respect to the liquid handling system and the image recognition system. The applied art of record does not teach or suggest this limitation.

Claim 121 has the limitation that the image recognition system is capable of determining varying cellular characteristics and the system controller regulates the biochamber

and liquid handling system in response to the determined cellular characteristics. The applied art of record does not teach or suggest this limitation.

Claim 122 has the limitation that the biochamber is respectively displaceable to both the liquid handling system and the image recognition system. The applied art of record does not teach or suggest this limitation.

Claim 123 has the limitation that the biochamber is dispensable along x and y lateral dimensions and the liquid handling system and image recognition system are disposable along a z dimension. The applied art of record does not teach or suggest this limitation.

In view of the foregoing amendments and remarks, it is respectfully requested that Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-124, now in this application be allowed.

Respectfully submitted,

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2/9/04
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